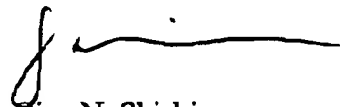


49). Unfortunately, in the "Remarks" section of that Amendment, it was erroneously stated that claims 1-17 and 19-48 were cancelled. In fact, claims 1-17 and 22-48 should have been cancelled and the added claims should be renumbered 49-113 instead of 50-114. Other than the renumbering, no amendments to the claims are necessary. A copy of the pending claims, as renumbered, is provided as Appendix A.

It is believed that no fee is due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10100104/GNS.

Respectfully submitted,



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**APPENDIX A:****PENDING CLAIMS AS OF SUPPLEMENTAL PRELIMINARY AMENDMENT**

18. A method of screening for a modulator of calpain function comprising:
- obtaining a calpain polypeptide;
  - determining a standard activity profile of the calpain polypeptide;
  - contacting the calpain polypeptide with a putative modulator; and
  - assaying for a change in the standard activity profile.
19. The method of claim 18, wherein the calpain polypeptide is a calpain 10 polypeptide.
20. The method of claim 18, wherein obtaining the calpain polypeptide comprises expressing the polypeptide in a host cell.
21. The method of claim 20, wherein the calpain polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.
49. The method of claim 19, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.
50. The method of claim 49, wherein the synthetic substrate is Suc-Leu-Tyr-AMC.
51. A method of screening for a modulator of calpain function comprising:
- obtaining an calpain polypeptide;
  - contacting the calpain polypeptide with a putative modulator; and
  - assaying for modulation of calpain function by the putative modulator.
52. The method of claim 51, wherein the calpain polypeptide is a calpain 10 polypeptide.

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53. The method of claim 52, wherein the calpain 10 polypeptide has a sequence comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.
54. The method of claim 51, further comprising determining a standard activity profile of the calpain polypeptide.
55. The method of claim 54, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.
56. The method of claim 55, wherein the synthetic substrate is Suc-Leu-Tyr-AMC.
57. The method of claim 55, wherein assaying for modulation of calpain function comprises assaying for a change in the standard activity profile.
58. The method of claim 51, wherein obtaining the calpain polypeptide comprises expressing the polypeptide in a host cell.
59. The method of claim 58, wherein the calpain polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.
60. The method of claim 51, wherein obtaining the calpain polypeptide comprises obtaining a cell containing the polypeptide.
61. The method of claim 60, wherein the cell is a pancreatic cell, a muscle cell, an adipose cell, or a liver cell.
62. The method of claim 61, wherein the cell is a pancreatic cell.

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63. The method of claim 62, wherein the pancreatic cell is comprised in an isolated pancreatic islet.
64. The method of claim 62, wherein the cell is a  $\beta$ -cell.
65. A method of screening for a modulator of calpain function comprising:
- a) obtaining an calpain-encoding nucleic acid segment;
  - b) determining a standard transcription and translation activity of the calpain nucleic acid sequence;
  - c) contacting the calpain-encoding nucleic acid segment with a putative modulator;
  - d) maintaining the nucleic acid segment and putative modulator under conditions that normally allow for calpain transcription and translation; and
  - e) assaying for a change in the transcription and translation activity.
66. The method of claim 65, wherein the calpain-encoding nucleic acid segment encodes calpain 10.
67. A calpain modulator prepared by a process comprising screening for a modulator of calpain function comprising:
- a) obtaining an calpain polypeptide;
  - b) determining a standard activity profile of the calpain polypeptide;
  - c) contacting the calpain polypeptide with a putative modulator; and
  - d) assaying for a change in the standard activity profile.
68. The modulator of claim 67, wherein obtaining the calpain polypeptide comprises expressing the polypeptide in a host cell.
69. The modulator of claim 67, wherein the calpain polypeptide is a calpain 10 polypeptide.
70. The modulator of claim 68, wherein the calpain polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

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71. The modulator of claim 67, wherein the modulator of calpain function is a modulator of a calpain polypeptide.
72. The modulator of claim 71, wherein the calpain polypeptide is a calpain 10 polypeptide.
73. The modulator of claim 72, wherein the calpain 10 polypeptide has a sequence comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.
74. The modulator of claim 67, wherein the modulator of calpain function is an agonist or antagonist of a calpain polypeptide.
75. The modulator of claim 74, wherein the modulator of calpain function is an inhibitor of a calpain polypeptide.
76. The modulator of claim 75, wherein the modulator inhibits calpain I and/or calpain II.
77. The modulator of claim 75, wherein the modulator is calpeptin.
78. The modulator of claim 75, wherein the modulator is calpain inhibitor 2 (ALLM).
79. The modulator of claim 75, wherein the modulator of calpain function is a protease inhibitor.
80. The modulator of claim 79, wherein the protease inhibitor is a thiol protease inhibitor.
81. The modulator of claim 80, wherein the thiol protease inhibitor is E-64-d.
82. The modulator of claim 67, further defined as a method comprising inhibiting calpain activity in a  $\beta$ -cell with a modulator of calpain function.

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83. The modulator of claim 67, further defined as a method comprising stimulating calpain activity in a muscle cell or fat cell with a modulator of calpain function.

84. The modulator of claim 67, further defined as a method comprising stimulating calpain activity in a fat cell or muscle cell with a modulator of calpain function and inhibiting calpain activity in a  $\beta$ -cell with a modulator of calpain function.

85. A calpain modulator prepared by a process comprising screening for a modulator of calpain function comprising:

- a) obtaining a calpain-encoding nucleic acid segment;
- b) determining a standard transcription and translation activity of the calpain nucleic acid sequence;
- c) contacting the calpain-encoding nucleic acid segment with a putative modulator;
- d) maintaining the nucleic acid segment and putative modulator under conditions that normally allow for calpain transcription and translation; and
- e) assaying for a change in the transcription and translation activity.

86. The method of claim 85, wherein the calpain-encoding nucleic acid segment encodes calpain 10.

87. A method of treating diabetes by modulating the function of one or more calpains in at least one of a  $\beta$ -cell, muscle cell, or fat cell with a modulator of calpain function, wherein the modulator is prepared by a process comprising screening for a modulator of calpain function comprising:

- a) obtaining a calpain-encoding nucleic acid segment;
- b) determining a standard transcription and translation activity of the calpain nucleic acid sequence;
- c) contacting the calpain-encoding nucleic acid segment with a putative modulator;
- d) maintaining the nucleic acid segment and putative modulator under conditions that normally allow for calpain transcription and translation; and

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- e) assaying for a change in the transcription and translation activity.

88. The method of claim 87, wherein the calpain-encoding nucleic acid segment encodes calpain 10.

89. A method of treating diabetes by modulating the function of one or more calpains in at least one of a  $\beta$ -cell, muscle cell, or fat cell with a modulator of calpain function, wherein the modulator is prepared by a process comprising screening for modulators of calpain function comprising:

- a) obtaining an calpain polypeptide;
- b) determining a standard activity profile of the calpain polypeptide;
- c) contacting the calpain polypeptide with a putative modulator; and
- d) assaying for a change in the standard activity profile.

90. The method of claim 89, wherein the modulator of calpain function is a modulator of a calpain polypeptide.

91. The method of claim 90, wherein the calpain polypeptide is a calpain 10 polypeptide.

92. The method of claim 91, wherein the calpain 10 polypeptide has a sequence comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.

93. The method of claim 90, wherein the modulator of calpain function is an agonist or antagonist of a calpain polypeptide.

94. The method of claim 90, wherein the modulator of calpain function is an inhibitor of a calpain polypeptide.

95. The method of claim 94, wherein the modulator inhibits calpain I and/or calpain II.

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96. The method of claim 94, wherein the modulator is calpeptin.
97. The method of claim 94, wherein the modulator is calpain inhibitor 2 (ALLM).
98. The method of claim 94, wherein the modulator of calpain function is a protease inhibitor.
99. The method of claim 98, wherein the protease inhibitor is a thiol protease inhibitor.
100. The method of claim 99, wherein the thiol protease inhibitor is E-64-d.
101. The method of claim 89, further defined as a method comprising inhibiting calpain activity in a  $\beta$ -cell with a modulator of calpain function.
102. The method of claim 89, further defined as a method comprising stimulating calpain activity in a muscle cell or fat cell with a modulator of calpain function.
103. The method of claim 89, further defined as a method comprising stimulating calpain activity in a fat cell or muscle cell with a modulator of calpain function and inhibiting calpain activity in a  $\beta$ -cell with a modulator of calpain function.
104. The method of claim 89, wherein the standard activity profile of the calpain 10 polypeptide is determined by measuring the binding of the calpain 10 polypeptide to a synthetic substrate.
105. The method of claim 104, wherein the synthetic substrate is Suc-Leu-Tyr-AMC.
106. The method of claim 104, wherein assaying for modulation of calpain function comprises assaying for a change in the standard activity profile.



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107. The method of claim 89, wherein obtaining the calpain polypeptide comprises expressing the polypeptide in a host cell.

108. The method of claim 107, wherein the calpain polypeptide is isolated away from the host cell prior to contacting the calpain polypeptide with the putative modulator.

109. The method of claim 89, wherein obtaining the calpain polypeptide comprises obtaining a cell containing the polypeptide.

110. The method of claim 109, wherein the cell is a pancreatic cell, a muscle cell, an adipose cell, or a liver cell.

111. The method of claim 110, wherein the cell is a pancreatic cell.

112. The method of claim 111, wherein the pancreatic cell is comprised in an isolated pancreatic islet.

113. The method of claim 111, wherein the cell is a  $\beta$ -cell.